REMARKS

Applicants have cancelled all of the previously pending claims, and have added new Claims 24-34. These claims define the invention with more particularity, and are believed allowable for the reasons explained below.

The present invention is a modified polysaccharide solution, which may include hyaluronic acid or some other polysaccharide. As is explained in the present specification, the ultimate purpose of the claimed composition is to make hydrophilic, lubricious coatings for devices that are inserted into the body. In order to make such coatings, the polysaccharide material must undergo crosslinking.

In a typical application, a coating made of the claimed modified polysaccharide solution is chemically bonded to another coating (sometimes called a tie coat, a base coat, or a primary coat) that is tightly adhered to a substrate. This chemical bonding preferably occurs by crosslinking and/or grafting.

In one example, the polysaccharide is hyaluronic acid. As has been explained fully in previous amendments in this application, the term "hyaluronic acid" has been used very loosely in the literature. Usually, what is really meant by this term is sodium hyaluronate.

Sodium hyaluronate or "hyaluronic acid" is a polymeric substance having a plurality of sodium cations, and a plurality of carboxyl groups. To enable the hyaluronic acid to become crosslinked, either to itself or to an underlying tie coat, at least some of the sodium ions must be stripped away, leaving free carboxyl sites which become available for participation in crosslinking reactions.

When "hyaluronic acid" (sodium hyaluronate) is modified such that some

of the sodium ions are stripped away to leave free carboxyl groups, the resulting modified composition has been termed a "free acid" in the present specification. What is meant by the term "free acid" is simply that some of the metal cations in the polysaccharide have been removed, freeing some of the functional groups (such as carboxyl groups, in the case of sodium hyaluronate) to participate in crosslinking reactions.

The modified composition of matter of the present invention is made according to a method which is described in the specification, and which has been patented in U.S. Patent No. 5,789,571. In the patented method, some of the metal cations are removed by the addition of a strong acid. In the case of sodium hyaluronate, the strong acid used is hydrochloric acid. The strong acid dissociates to produce an anion in the solution. In the case of sodium hyaluronate and hydrochloric acid, this anion is chloride. It is a feature of the modified composition that it is substantially free of this anion. It has been found that the presence of this anion, which is, in effect, the residue of the treatment with the strong acid, is likely to interfere with, or even nullify, the effect of crosslinking agents.

Thus, to produce the desired bilaminar, lubricious coatings, it is necessary to provide a polysaccharide solution not only in which the polysaccharide has functional groups which are freed to participate in crosslinking reactions, but also in which the anion residue of the acid used to free those functional groups has been substantially removed, so as not to interfere chemically with the crosslinking reactions.

The present invention therefore claims a "free acid" form of a polysaccharide, which is a composition of matter that is suitable for crosslinking, and is therefore useful in making the bilaminar, lubricious coatings described above.

New Claim 24 recites a composition of matter that comprises a water-soluble polysaccharide having functional groups which facilitate crosslinking. Support for this terminology is found in the specification, such as in the paragraph beginning on page 7, line 26 through page 8, line 11. The latter passage discusses the carboxyl groups which, in the case where the polysaccharide is hyaluronic acid, provide the functionality necessary for crosslinking.

Claim 24 recites steps of the process described in the specification, and also recites that the solution comprising the final product is substantially free of the anion formed from the acid which is mixed with the polysaccharide, and that the product solution has a pH which is less than about 4. Support for the former limitation is found in the specification, which teaches that the final product, in the case where the acid is hydrochloric acid, is free of the chloride ion (see page 5, lines 1-3; page 6, lines 8-9; page 9, lines 20-21; page 12, lines 4-5 and line 13). Since the specification makes clear that other strong acids could be used instead of hydrochloric acid (see page 8, lines 12-15), it is apparent that the teaching of the specification is to remove whatever anion has been provided by the acid.

The limitation concerning the pH of the final product is supported throughout the specification. For example, page 5, lines 4-5 states that the product had a pH of about 3.0-3.5. The product made in Example 2 (page 6) had a pH of 3.0. The product made in Example 4 (page 9) had a pH of about 3.2. The product made in Example 5 (page 11) had a pH of about 3.9. The product made in Example 6 (page 12) had a pH of about 3.7. And the product made in Example 7 (page 12) had a pH of about 3.4.

New Claim 25 recites three specific polysaccharides which can be used to make the composition of the present invention. Sodium hyaluronate is

described in Examples 1-4. Chondroitin sulfate is described in Examples 5 and 6. Example 7 uses sodium carboxymethyl cellulose.

New Claims 26 and 27 define the acid that is mixed with the initial polysaccharide solution. The list of acids is supported by the specification at page 8, lines 12-15.

New Claims 28-30 are specific to particular polysaccharides, and recite the respective pH values obtained from experiments. The recitations in these claims are supported by the examples in the specification, as explained above.

New Claim 31 recites a modified form of hyaluronic acid, as described above. The recited product is an aqueous solution of hyaluronic acid having a plurality of carboxyl groups, some of which have been converted to the free acid form. The fact that hyaluronic acid includes carboxyl groups is not only an inherent feature of hyaluronic acid, but it is also described in U.S. Patent No. 4,801,475 (column 4, lines 25-28), which has been incorporated by reference into the specification. The fact that some of these carboxyl groups have been converted to the free acid form is supported by the present specification at page 10, lines 14-25. The latter passage states that not all of the components of the polysaccharide need be converted to free carboxylic acid forms, and that only a few grafting points may be sufficient to anchor the polysaccharide top coat to the primary coat (tie coat). Thus, the passage states, fewer than all of the carboxylic acid sites will be converted to the free acid form. Claim 31 also recites the pH limitation discussed above, and recites that the product is free of ions that would come from any of the strong acids listed above.

New Claim 32 is another independent product claim, which recites a

modified form of hyaluronic acid. This claim recites the fact that the solution has been mixed with a strong acid which produces an anion, and that the anion has been removed from the final product. These features are clearly supported by the specification for the reasons given above. New Claim 33 recites that the strong acid is selected from the group of acids listed in the specification.

The method limitation in Claim 32 is pertinent to the physical properties of the claimed composition. As explained above, any residue of the strong acid anion will likely interfere with the crosslinking reaction. To make a useful product, the anion must be removed. Thus, it is important that the composition be free of the anion of the acid which was previously mixed with the initial polysaccharide.

The experimental data in the present specification prove that the method limitation discussed above critically affects the properties of the final product. That is, the product made by the claimed process is truly different from any known product of the prior art. In particular, the attention of the Examiner is drawn to Example 3, which compares the results from three cases, labeled A, B, and C. As stated in the specification, on page 7, lines 4-9, the material produced in Case C was not made according to a method that included mixing the polysaccharide with a strong acid. The resulting material was unsatisfactory, in contrast with the material produced with the use of the strong acid.

New Claim 34 recites the invention as a modified form of a polysaccharide, in an aqueous solution, the polysaccharide having a plurality of functional groups which are bound to an alkali metal cation. (In the case where the polysaccharide is hyaluronic acid, the alkali metal cation is sodium.) At least on some of the functional groups, the alkali metal cation has been replaced with a hydrogen ion. The latter statement

is equivalent to reciting the conversion of the group to its free acid form, and is a direct chemical consequence of mixing the polysaccharide solution with a strong acid. The claim also contains the pH limitation discussed above, as well as the limitation that anions corresponding to a strong acid are absent from the final product.

The Examiner has rejected the claims under 35 U.S.C. §102, in view of the Merck Index and the article by Meyer. Applicants submit that the present characterization of the invention, as recited in the new claims, renders these references irrelevant. The Merck Index clearly says nothing about a modified hyaluronic acid, having the claimed properties, and provides no suggestion for making the claimed product. The same is true of the article by Meyer, which gives only a general description of "hyaluronic acid", but which does not teach or suggest the modified product now claimed.

The same conclusion applies to the other references cited by the Examiner, but not applied to the claims.

Therefore Applicants submit that the claims define patentably over all of the known references. Applicants have developed a composition of matter that is indeed different from any composition previously known. The composition invented by Applicants makes it possible to form highly lubricious, biocompatible coatings on the surfaces of devices that are intended to be inserted into the body, and therefore represents a substantial advance over the state of the art at the time the invention was made.

For all of the above reasons, Applicants submit that all of the pending claims are allowable.